REMARKS

Specification Amendments

The specification has been amended to correctly recite that the subject application is a continuation-in-part of U.S. Application 09/909,122 filed July 19, 2001. A Declaration for Patent Application was filed on May 15, 2002. In an abundance of caution, a Supplemental Declaration will be filed separately in the subject application.

The specification has also been amended to correct a typographical error, namely to replace "Try" with "Tyr". It is noted that "Try" is not an abbreviation for any amino acid. No new matter is added by this amendment to the specification.

New Claims 47-54

The subject matter of new Claims 47-54 is fully supported in the present application as filed January 16, 2002. Support can be found in the specification, for example, at page 2, lines 23-24; page 3, lines 3-15; page 3, lines 20-24; page 4, lines 19-20; page 8, line 1-3; page 9, line 22 to page 10, line 23; page 14, lines 8-10; in originally filed Claims 2-3, 13-18 and 44-46.

New Claims 47, 53 and 54 recite the same peptide as in original Claims 14-15 and 44-46, i.e., amidated at the C-terminus with $-NH_2$. However, the nomenclature used to represent this peptide in new Claims 47, 53 and 54 is more commonly used in the art. That is, a molecule amidated with "$-NH_2$" at the C-terminus means that the -COOH group at the C-terminus is replaced with $-CONH_2$.

No new matter has been added by new Claims 47-54.

Substitute Sequence Listing

Transmitted concurrently herewith is a copy of a Substitute "Sequence Listing" in paper form (sheets 1/3 through 3/3) comprising SEQ ID NOs: 1 through 7 for the above-identified patent application as required by 37 C.F.R. §§ 1.825(a) and 1.821(c), and a copy of the Substitute "Sequence Listing" in computer readable form as required by 37 C.F.R. §§ 1.825(b) and 1.821(e). Please replace the "Sequence Listing" filed on January 5, 2004 (sheets 1/3 through 3/3) with the attached Substitute "Sequence Listing".

The Substitute "Sequence Listing" filed concurrently herewith recites that SEQ ID NO: 6, which consists of the 23 amino acid sequence Ala-Gly-Tyr-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly-Asp-Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val, has an amide at the *C*-terminus. Support for SEQ ID NO: 6 is found in the specification, for example, at page 8, lines 1-3, where it is stated that SEQ ID NO: 6 has the identical amino acid sequence of SEQ ID NO: 5 and also contains a *C*-terminal amide.

The Substitute "Sequence Listing" filed concurrently herewith also adds SEQ ID NO: 7, which had been inadvertently omitted from the "Sequence Listing" filed on January 5, 2004. SEQ ID NO: 7 consists of the 23 amino acid sequence Ala-Gly-Tyr-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly-Asp-Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val and is amidated with NH_2 at the *C*-terminus. Support for SEQ ID NO: 7 is found in the specification, for example, in originally filed Claims 15, 39-40 and 44-46, where the amino acid sequence Ala-Gly-Tyr-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly-Asp-Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val-$CONH_2$ is recited.

The Substitute "Sequence Listing" also recites nomenclature that is more commonly used in the art for SEQ ID NO: 7. That is, a molecule amidated with "-NH_2" at the *C*-terminus means that the -COOH group at the *C*-terminus is replaced with -$CONH_2$. No new matter has been added with the Substitute "Sequence Listing".

As required by 37 C.F.R. § 1.825(b), Applicants' Attorney hereby states that the contents of the Substitute "Sequence Listing" in paper form and in the computer readable form submitted herewith are the same and, as required by 37 C.F.R. § 1.825(a), also states that the submission includes no new matter.

"Amide"

The use of the term "amide" in the subject application is in accordance with the definition recognized and accepted by those skilled in the art. Specifically, the term "amide" is understood in the art to define a functional group generically. A molecule amidated with "-NH_2" at the *C*-terminus (i.e., wherein the -COOH group at the *C*-terminus is replaced with -$CONH_2$) is one example of an amide.

Information Disclosure Statement

A Supplemental Information Disclosure Statement (IDS) is being filed concurrently herewith. Entry and consideration of the IDS are respectfully requested.

Statutory Double Patenting

Claims 1-5, 11-19 and 41-46 stand provisionally rejected under 35 U.S.C. § 101 as claiming the same invention as that of Claims 1-5, 11-16, 35-43 of co-pending Application No. 09/909,122.

Claims 1-5, 11-19 and 41-46 have been cancelled, thereby rendering this provisional rejection under 35 U.S.C. § 101 moot.

Rejection of Claims 1-5, 11, 12, 19 and 41-43 Under 35 U.S.C. § 102(b)

Claims 1-5, 11, 12, 19 and 41-43 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Simmons *et al.* (*Calcium Metabolism: Comparative Endocrinology*, International Satellite Symposium, 2nd, San Francisco, CA, November 30, 1998).

Applicants respectfully disagree that Claims 1-5, 11, 12, 19 and 41-43 are anticipated by the teachings of Simmons *et al.* for the reasons of record. However, in an effort to advance prosecution in the subject application and without acquiescing to the Examiner's rejection, Claims 1-5, 11, 12, 19 and 41-43 have been cancelled, thereby rendering this rejection moot.

New independent Claims 47, 53 and 54 recite that the peptide Ala-Gly-Tyr-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly-Asp-Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val-NH_2 (SEQ ID NO: 7) is administered in a method to stimulate bone growth in a subject at a site in need of bone growth and at which bone growth would not occur if left untreated or at a site in need of a bone graft. New Claims 48-52 are dependent on Claim 47 and thus, carry the limitations of Claim 47.

Simmons *et al.* teach that TP508 enhanced the mechanical strength and accelerated the progression of rat femoral fracture healing. Healing of this fracture (bone regeneration) was occurring prior to TP508 treatment, indicating that treatment (including bone grafting and osteoinduction) was not required for normal bone growth. Thus, Simmons *et al.* teach that TP508 enhanced the mechanical strength and accelerated the rate of *normal* fracture healing in a

fracture that normally heals without treatment. Simmons *et al.* do not teach or suggest the use of TP508 for stimulating bone formation at a site in need of bone growth and at which bone growth would not occur if the site was left untreated. As such, new Claims 47-54 are not anticipated by the Simmons *et al.* reference.

Rejection of Claims 16-18 Under 35 U.S.C. § 103(a)

Claims 16-18 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Simmons *et al.* in view of Schmitz (U.S. Patent No. 4,637,931).

Applicants respectfully disagree that Claims 16-18 are unpatentable over the cited art for the reasons of record. However, in an effort to advance prosecution in the subject application and without acquiescing to the Examiner's rejection, Claims 16-18 have been cancelled, thereby rendering this rejection moot.

As indicated above, new independent Claims 47, 53 and 54 recite that the peptide Ala-Gly-Tyr-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly-Asp-Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val-NH_2 (SEQ ID NO: 7) is administered in a method to stimulate bone growth in a subject at a site in need of bone growth and at which bone growth would not occur if left untreated or at a site in need of a bone graft. New Claims 48-52 are dependent on Claim 47 and thus, carry the limitation of Claim 47.

The cited references (Simmons *et al.*, Schmitz), alone or in combination, would not have suggested the claimed invention, as set forth in new Claims 47-54, to one of ordinary skill in the art at the time the invention was made with a reasonable expectation of success. More specifically, the cited references, alone or in combination, would not have suggested, with reasonable expectation of success, the use of a NPAR agonist in a method of stimulating bone growth in a subject at a site in need of bone growth and at which bone growth would not occur if left untreated. Simmons *et al.* teach that TP508 can be used in enhancing the mechanical strength and accelerating the rate of *normal* fracture healing in a fracture that normally heals without treatment. Schmitz teaches the use of a bone repair material consisting of decalcified freeze-dried bone and biodegradable biodegradable, biocompatible copolymer for improving and accelerating the healing of osseous tissue. Importantly, neither reference teaches or suggests that

NPAR agonists, including TP508, can stimulate bone growth within a subject at a site in need of bone growth and at which bone growth would not occur if the site was left untreated. In fact, prior to Applicants' results described in the subject application, one of ordinary skill in the art would not have reasonably expected that NPAR agonists could be used successfully to stimulate bone formation at a site in need of bone growth and at which bone growth would not occur if the site was left untreated.

Rejection of Claims 1-5, 11-19 and 41-46 Under 35 U.S.C. § 112, First Paragraph (Enablement)

Claims 1-5, 11-19 and 41-46 stand rejected under 35 U.S.C. § 112, first paragraph, because, in the Examiner's assessment, the specification does not provide enablement for the use of any agonist of the non-proteolytically activated thrombin receptor in the claimed methods of stimulating bone growth at a site in a subject in need of osteoinduction or bone grafting. However, the Examiner acknowledges that the specification is enabling for the use of "an agonist of the non-proteolytically activated thrombin receptor wherein the agonist is a thrombin derivative comprising a polypeptide 23 amino acids in length and is represented by the following structure Arg-Gly-Asp-Ala-R wherein R is a serine esterase conserved sequence and wherein Asp-Ala of said structure comprise the first two amino acids of the serine esterase conserved sequence" or "an agonist comprising SEQ ID NO:5" or "an agonist comprising SEQ ID NO:6" (Paper No. 20040323, at page 7, line 18 to page 8, line 7).

Applicants respectfully disagree with the instant rejection for the reasons of record. However, in an effort to advance prosecution in the subject application and without acquiescing to the Examiner's rejection or waiving the right to prosecute the full scope of the original claims in the future, Claims 1-5, 11-19 and 41-46 have been cancelled, thereby rendering the rejection moot.

Rejection of Claim 1-4 Under 35 U.S.C. § 112, First Paragraph (Written Description)

Claims 1-4 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one

skilled in the art that Applicants had possession of the claimed invention at the time the application was filed.

Applicants respectfully disagree with the instant rejection for the reasons of record. However, in an effort to advance prosecution in the subject application and without acquiescing to the Examiner's rejection or waiving the right to prosecute the full scope of the original claims in the future, Claims 1-4 have been cancelled, thereby rendering the rejection moot.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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